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ENHANCE CRT
CRT Implant Strategy Using the Longest Electrical Delay for Non-Left Bundle Branch Block Patients – A Prospective, Randomized Post-Market Pilot Study
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Sponsor

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STUDY PROTOCOL
FOR THE

CRT IMPLANT STRATEGY USING THE LONGEST
ELECTRICAL DELAY FOR NON-LEFT BUNDLE
BRANCH BLOCK PATIENTS
(ENHANCE CRT)
A PROSPECTIVE, RANDOMIZED POSTMARKET PILOT
STUDY

August 19, 2013

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1.0 Introduction

Numerous clinical studies have evaluated the benefits of biventricular pacing compared to optimal medical therapy^{1,2}. However, some patients, who have undergone a successful implantation of a biventricular pacing device, do not have a measurable improvement in cardiac performance or symptoms³. Such patients are generally considered to be CRT non-responders. Clinical studies have suggested that there may be many factors that contribute to the non-responder rate and there is a considerable degree of interpatient and inpatient variability. Some of these factors include the absence of significant areas of dyssynchrony prior to device implantation, etiology of heart disease (ischemic versus nonischemic), coronary sinus lead position, and inadequate device programming based on patient-specific physiology⁴. An ongoing area of important investigation for CRT is to reduce the non-responder rate.

Historically, CRT response in RBBB patients has not been as positive as it has been for LBBB patients.⁵ Early studies assessing the impact of LV lead position on the non-responder rate have suggested that the ideal lead position is in the lateral or posterolateral wall.^{6,7} The lateral or posterolateral wall lead position has worked well in LBBB patients.⁸ The same anatomical implant strategy may or may not be effective for RBBB patients as evidenced by the high nonresponder rate.

The anterior vein may be an alternative LV lead location for nonresponders. Research has shown that the anterior vein has not been a popular choice for LV lead placement in the past.⁹ The lack of use may be due to its proximity to the right ventricle. Physicians have tried to circumvent this issue by placing the lead as basal as possible in the anterior vein to stimulate the left ventricle and promote CRT. Research has shown that if the LV lead is successfully placed in the middle or basal portion of the anterior vein, then there isn't an increase in heart failure or death.¹⁰ The downfall of this strategy is that when the distal end of the lead is placed in the basal portion of the anterior vein, then the LV lead is not anchored securely in the anterior vein. The usefulness of the anterior vein in CRT can be evaluated with the four electrodes that are available on the Quartet LV lead. The physician can program the basal electrode of the Quartet LV lead while securely anchoring the distal portion of the LV lead in the apex of the anterior vein.

QRS widening and morphology changes are associated with ventricular dyssynchrony. A substudy of the MADIT-CRT trial investigated whether LBBB and non-LBBB patients with a wide QRS (≥ 130 ms) benefit from CRT. Patients with LBBB, wide QRS and CRT had slower heart failure progression and decreased risk of ventricular tachyarrhythmias. Non-LBBB patients with wide QRS did not experience any clinical benefit from CRT.¹¹ A substudy of the CARE-HF trial examined whether electrocardiographic characteristics at baseline can predict long term health outcomes. While LBBB and RBBB were not independent predictors of mortality and unplanned hospitalizations, the results revealed that the presence of RBBB is associated with higher mortality and unplanned hospitalization than the presence of LBBB¹². The authors note that the poor outcome of the RBBB patients could be due to non-response to CRT.

Utilizing the site of the latest electrical activation in the left ventricle may be an effective strategy to reduce the nonresponder rate in RBBB patients. Intraventricular conduction delays can lead to and exacerbate existing dyssynchronous left ventricular contraction, which occurs in up to 30% of patients with heart failure caused by dilated cardiomyopathy¹³. Research in LBBB patients has shown that choosing the pacing site with the longest electrical LV delay at implant can lead to long-term event free survival at 1 year of follow up¹¹. In a subset of patients with LBBB and non-LBBB from the SMART AV trial, investigators have also successfully demonstrated that choosing the pacing site with the largest amount of dyssynchrony as measured by LV electrical delay, also called QLV, was strongly associated with reverse remodeling and quality of life improvement. The QLV was measured as the interval from the onset of the QRS from the surface ECG to the first large peak of the LV electrogram. The authors suggest that choosing the longest QLV within a vein or a different vein at implant is a reasonable strategy to improve CRT outcomes¹⁴.

A quadripolar lead has the unique characteristics to perform the QLV measurement and provide the programming flexibility that is needed for anterior LV lead placement. The Quartet lead has four cathodes (Distal tip, Mid 2, Mid 3 and Proximal 4). The four cathodes can be programmed in ten different pacing configurations using the Merlin programmer. The programmability of the Quartet lead provides an opportunity to determine if the anterior interventricular vein can be a good vessel of choice for pacing when selected according to the longest electrical LV delay as compared to a non-anterior vein location in a non-LBBB patient population.

2.0 Purpose

The purpose of this study is to analyze the effect of LV lead pacing location (guided via QLV measurement vs. standard of care approach) in the non-LBBB HF patient population. This pilot study will provide preliminary feasibility data on QLV-based implant strategy in a non-LBBB patient population.

This study is sponsored by St. Jude Medical (hereinafter referred to as SJM) and uses market approved product and technologies (Quartet LV lead with Unify Quadra™, Quadra Assura™ CRT-D or any market approved CRT-D device with quadripolar pacing capabilities).

3.0 Clinical Protocol

3.1 Study Design and Scope

This is a prospective, pilot, multi-center, double-blinded, randomized postmarket study to assess the effect of LV lead pacing location (guided via QLV measurement vs. standard of care approach) in non-LBBB patients.

In the QLV arm the physician will:

- 1) Assess two branches of the coronary sinus (A non-traditional vessel (inclusive of the anterior region) will be tested first and a traditional free lateral branch will be tested second for LV lead placement.
- 2) Measure QLV for each of the four cathodes in each branch,
- 3) Choose the vein branch and cathode with the longest QLV measurement and program a vector based on that cathode. If there are multiple cathodes with relatively long QLV measurements, then the physician should first choose the cathode with the longest QLV. The physician will then test that cathode for phrenic nerve stimulation with a 10V output. If that cathode has signs of positive phrenic nerve stimulation, then move to the cathode that gives the second longest QLV. The physician will continue the electrical testing until he finds a cathode that does not have phrenic nerve stimulation.

In the standard of care group, the LV lead placement will be carried out according to the physician's standard of care implant approach.

The impact of the LV lead position will be evaluated based on the patient's response to CRT utilizing the clinical composite endpoint (all cause mortality, heart failure (HF) hospitalizations, NYHA class, and patient global assessment). A Clinical Events Committee (CEC) will adjudicate HF hospitalizations. Authorized site personnel conducting the NYHA Class assessment and patient global assessment will be blinded to the randomization assignment and lead implant.

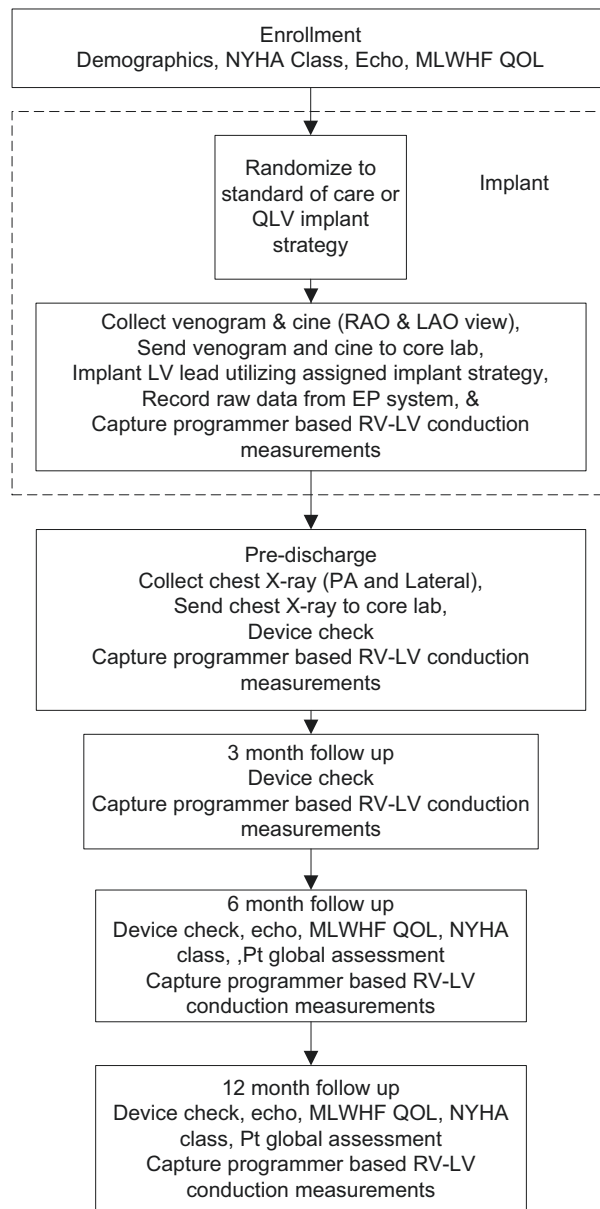
The study will be conducted at up to 40 centers. A maximum of 50 enrollments will be allowed per center. A total of 220 patients is required to complete their 12 month visit. The total sample size for the study is set at 250 patients to account for attrition.

Enrollment in this study is expected to take approximately 12-15 months. The anticipated duration of this study is 24-27 months, depending on the rate of enrollment. All patients will be implanted with a Quartet lead.

The following study evaluations will occur after implant: pre-discharge, 3 months, 6 months, and 12 months. Follow up schedules will be calculated from the date of successful implant



Figure 1: Study Flow Diagram



3.2 Objectives/Study Endpoints

The primary endpoint of this pilot study is to evaluate the clinical composite score¹⁵ at 12 months in non-LBBB patients using a standard of care versus latest electrical delay (QLV) based implant strategy. This pilot study will provide preliminary feasibility data on the use of a QLV-based implant strategy in a non-LBBB patient population.

The CCS includes 4 components: NYHA class, Patient Global Assessment (PGA), HF events, and cardiovascular death. An independent Clinical Events Committee (CEC) will adjudicate the HF events.

In this trial a **HF event** is defined as any one of the following when the subject has symptoms and/or signs consistent with congestive heart failure:

- Hospitalization for HF ≥ 24 hours
- Clinic or hospital visit for HF < 24 hours (i.e. outpatient treatment, observational care, ER, Urgent Care and physician's office visit) requiring administration of IV diuretics, inotropes, and/or vasodilators

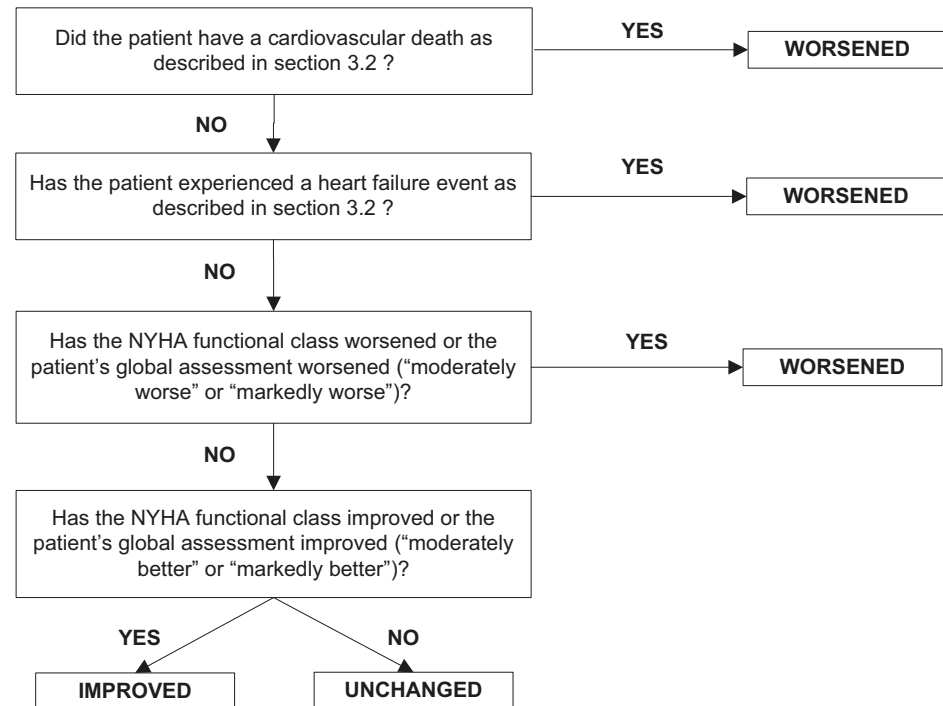
A Mortality Committee will review and classify all patient deaths. The committee will classify deaths based on primary organ cause and will classify deaths as cardiac, noncardiac or unknown.¹⁶ A **cardiovascular death** in this trial is defined as a death that was classified as cardiac by the Mortality Committee.

Using the CCS and the Decision algorithm described in Figure 2 below, the patients are categorized as Improved, Worsened or Unchanged based on the following rules.

- "Improved" – patients that demonstrate:
 - At least a one-class improvement in NYHA Class OR improvement by PGA ("better" or "markedly better")
AND
 - No HF events as described above
AND
 - No cardiovascular death
- "Worsened" – patients that demonstrate:
 - Worsening in NYHA Class OR worsening by PGA ("worse" or "markedly worse")
OR
 - Presence of HF events as described above
OR
 - Cardiovascular death

- “Unchanged” – patients that are neither “Improved” nor “Worsened”.

Figure 2: Decision algorithm to classify response to CRT treatment



3.2.1 Hypothesis

The hypothesis for the clinical composite score endpoint at 12 months is formulated as:

$$H_0: p_{QLV} \leq p_{con}$$

$$H_a: p_{QLV} > p_{con}$$

where p_{con} and p_{QLV} are percentages of patients with improved clinical composite score for patients with standard of care implant strategy and QLV implant strategy at 12 months, respectively. Using this endpoint, patients were classified into one of three response groups: Improved, Unchanged or Worsened based on the rules stated above.

Analysis:

The hypothesis will be tested at the 5% significance level using the one-sided Fisher’s Exact Test.

3.2.2 Additional Data

- ♦ Demographics
- ♦ QLV measurements (see Appendix C) in both groups and QLV as a percentage of the QRS (Data will be analyzed by a QLV core lab)
- ♦ QRS duration and morphology (RBBB, RB/LAFB, RB/LPFB, and NS-IVCD)
- ♦ RVpace-LV sense conduction measurements (see Appendix E)
- ♦ Electrical signals from the raw data recording of the EP system during implant
- ♦ Minnesota Living with Heart Failure Quality of Life Questionnaire (MLWHF QOL)
- ♦ Patient Global Assessment
- ♦ Echo measurements (LVESV index, LVEF, LVEDV, and LVESV)
- ♦ Heart Failure Hospitalizations
- ♦ Total fluoroscopy time
- ♦ Mortality
- ♦ Venous angiograms

3.3 Patient Selection

3.3.1 Inclusion Criteria

Eligible patients will meet **all** of the following:

1. Have non-LBBB morphology (includes complete RBBB and IVCD with a QRS duration ≥ 120 ms)
2. Have the following indication per the 2013 updated ACCF/AHA/HRS guidelines:
 - a. $LVEF \leq 35\%$, sinus rhythm, ischemic or non-ischemic cardiomyopathy, a non-LBBB pattern with QRS duration ≥ 120 ms, and NYHA class III/ambulatory class IV on guideline directed medical therapy (GDMT).
3. Receiving a new CRT implant or undergoing an upgrade from an existing ICD or pacemaker implant with no more than 10% RV pacing
4. Are 18 years or older, or of legal age to give informed consent specific to state and local law
5. Ability to provide informed consent for study participation and is willing and able to comply with the prescribed follow-up tests and schedule of evaluations

3.3.2 Exclusion Criteria

Patients will be excluded if they meet **any** of the following:

1. Irreversible occlusion of venous access that will prevent placement of the CRT-ICD system either through the right or left upper extremity venous system.
2. Undergoing left ventricular lead placement via a surgical or epicardial approach.
3. Cardiomyopathy due solely to valvular disease that is not repaired/replaced
4. Enrolled or intend to participate in a clinical drug and/or device study, which could confound the results of this trial as determined by SJM, during the course of this clinical study.
5. Left bundle branch block (LBBB): QRS width ≥ 120 ms, with predominantly negative QRS in lead V1, and upright, monophasic QRS in leads I and V6.
6. Incomplete RBBB
7. IVCD with a QRS duration between 110 and 119ms
8. Persistent or Permanent atrial fibrillation.
9. Pacemaker dependent.
10. Patients who are being upgraded primarily due to RV pacing.
11. Women who are pregnant or who plan to become pregnant during the clinical trial.
12. Life expectancy < 1 year

3.4 Study Procedures

All required study procedures at each specified interval are outlined in the sections below. Refer to Table 1 for an overview of the required study procedures at each interval or study visit.

Table 1: Schedule of Evaluations Summary

Evaluation	Enrollment	Implant	Pre-Discharge	3 months	6 months	12 months
Inclusion/ exclusion evaluation	√					
Medical history/cardiac medications	√					
Chest X-ray			√			
Venous Angiogram/Venogram in RAO & LAO		√				
Cine Fluorography		√				
Randomization ¹		√				
QLV measurements during implant ²		√				
Collection of raw electrical data from EP system ²		√				
QLV measurements with programmer ²			√	√	√	√
RV pace-LV sense conduction measurements with Merlin programmer ³		√	√	√	√	√
LV lead capture threshold testing (with pulse width of 0.5ms) and pacing lead impedance in final programmed vector ³		√	√	√	√	√
NYHA Class	√				√	√
2D Echocardiogram	√ ⁴				√	√
MLWHF QOL	√ ⁵				√	√
Patient Global Assessment					√	√

¹ Patient can be randomized up to 24 hours before implant.

² QLV randomized group only

³ Both QLV and standard of care group.

⁴ This procedure can be done up to 30 days prior to implant

⁵ This procedure can be done up to 7 days prior to implant

3.4.1 Data Entry

Each study center will capture all study-related data and submit via the electronic data capture (EDC) system. All study data will be entered and submitted through this system, including device data. Device session records and source documents can also be submitted through this system. Training on how to access the system and how to submit CRFs and other forms will be provided prior to beginning the study.

3.4.2 Enrollment Requirements

All patients will be considered for participation in this study regardless of gender. Patients will undergo screening evaluations as outlined by the inclusion/exclusion criteria. Data will be collected on the patient's gender, age, height, weight, ethnicity, race, cardiac disease history, arrhythmia history, smoking history, cardiac medications, indication for CRT-D implant, NYHA class (Appendix A), and QRS duration.

The cardiologist performing the NYHA class assessment will not be aware of the randomization assignment. This blinding scheme will reduce the effect of bias on the part of the testing personnel.

Patients who meet the following conditions will be considered enrolled in the study.

- Meet inclusion/exclusion criteria
- Sign an IRB approved informed consent
- Have an attempted implant of a Quadripolar CRT-D system (device and lead)

The enrollment date for patients in the study will be the date of implant. Patients who have an attempted implant of the Quartet™ LV lead and device will be considered enrolled in the study.

A 2D echocardiogram will be performed. The patient will complete a Minnesota Living with Heart Failure Quality of Life (MLWHF QOL) questionnaire (Appendix B). After the patient signs the informed consent, the echocardiogram can be completed up to 30 days prior to implant and the MLWHF QOL can be completed up to 7 days prior to implant.

An Enrollment, Medical History, Echo and Minnesota Living with Heart Failure Case Report Form will be completed and submitted. If a protocol deviation occurred during this visit, complete a Deviation Case Report Form. Submit the electronic forms to St. Jude Medical, using the EDC system.

3.4.3 Implant

3.4.3.1 Randomization

Randomization will be assigned in a 2:1 ratio between the QLV implant strategy and standard of care anatomical implant strategy groups. Randomization can occur up to 24 hours prior to the implant procedure via web-based randomization system provided by St. Jude Medical.

3.4.3.2 Blinding

The study will be double-blinded. The patients and the site personnel that conduct the NYHA class assessments and Patient Global Assessment will be blinded to the randomization assignment. The implanting physician will not be blinded to the randomization assignment. The NYHA class assessment and patient global assessment will be performed by a cardiologist that did not implant the device.

The independent CEC will remain blinded to patient and site identifiers.

3.4.3.3 Implant Procedures

Consult the User's Manual for implantation guidelines, appropriate lead/device connections and general handling information.

3.4.3.4 Left Ventricular Lead Placement

3.4.3.4.1 LV lead placement for QLV-based implant strategy

In the QLV-based group the following procedure will be followed:

To facilitate the introduction of the Quartet™ Model 1458Q left heart lead into the coronary sinus, the physician can use any appropriate delivery system that is legally marketed from SJM or other manufacturers. A venous angiogram/venogram in both RAO and LAO at 20-40° views will be done to assess the coronary sinus branch anatomy before the lead placement. Cinefluoroscopy post-LV lead placement in both RAO and LAO at the same angles as the venograms should be recorded. The venous angiogram/venogram/ cinefluoroscopy will be sent to the core lab for evaluation.

Follow QLV measurement instructions. (Appendix C). The QLV measurements from each patient will be sent to a QLV core lab for validation purposes. Record raw data from EP system during implant procedure.

3.4.3.4.2 LV lead placement for standard of care implant strategy

In the standard of care group the implanting physician will carry out the procedure according to the standard of care (i.e. lateral branch). To facilitate the introduction of the Quartet™

Model 1458Q left heart lead into the coronary sinus, the physician can use any appropriate delivery system that is legally marketed from SJM or other manufacturers. The physician will also test the system at 10V output to assess for phrenic nerve stimulation. Record raw data from EP system during implant procedure.

QLV measurements will not be used. A venous angiogram/venogram in both RAO and LAO at 20-40° views will be done to assess the coronary sinus branch anatomy before the lead placement. Cinefluoroscopy post-LV lead placement in both RAO and LAO at the same angles as the venograms should be recorded. The venous angiogram/venogram/ cinefluoroscopy will be sent to the core lab for evaluation.

3.4.3.5 Electrical Measurements at Implant

After the device is connected to the leads, the following electrical measurements should be performed for both groups:

- Complete “RV Pace – LV Sense” conduction measurements (Appendix E)
- For the final programmed vector of the LV lead:
 - Capture threshold testing using a pulse width of 0.5ms
 - Lead impedance

An Implant Case Report Form should be completed. If an adverse event occurred during the implant procedure, an Adverse Event Case Report Form will be completed. Completed forms and cine venogram fluoroscopy should be submitted electronically through the EDC system to St. Jude Medical, IESD.

A printout demonstrating the QLV measurement via the EP recording system for all 4 cathodes of the LV lead (QLV randomized patients only) will be submitted to SJM.

Export the device session records after all required testing has been performed, and submit to SJM using the EDC system. The device session records will include:

1. Initial and Final Programmed Parameters
2. Real-Time Measurements and Trends for the LV leads
3. Capture threshold testing for the LV leads
4. All stored EGM(s)
5. RV pace-LV sense conduction measurements

3.4.3.6 Unsuccessful Implant

If an unsuccessful implant occurs, then the physician may re-attempt the implantation of a SJM Quadripolar system via an endocardial approach per his/her discretion. If the physician chooses to re-attempt the implantation of SJM Quadripolar system, an Implant, Adverse Event (if applicable), and Out of Service (if applicable) Case Report Forms should be completed.

Patients who meet the following conditions will be withdrawn from the study:

- Unsuccessful implant (e.g. Quartet LV lead is not implanted) and a non-endocardial approach for LV lead placement is planned
- Unsuccessful implant (e.g. Quartet LV lead is not implanted) and no re-attempt is planned

Implant, Out of Service (if applicable), and Withdrawal Case Report Forms will be completed.

3.5 Follow Up

Patients who have a successful system implant will be seen at the following visits: pre-discharge, 3 months, 6 months, and 12 months.

The schedule of the follow-up visits is based on the date of the successful LV lead implant. Table 2 outlines the time window that is permitted for each of the study interval visits.

In all follow-up visits, please record all device interrogation data.

Table 2: Study Interval Time Windows

Pre-discharge	+ 7 days
3 months	± 14 days
6 month	± 30 days
12 months	± 45 days

3.5.1 Pre-discharge visit

At the Pre-discharge visit only, a PA and Lateral view chest x-ray of the final lead position will be done for all patients. A digital copy of the x-ray should be submitted to the core lab for evaluation.

For patients that are randomized to the QLV-based implant strategy, QLV measurements will be completed with the programmer

1. During device follow up, gather a QLV measurement for each of the 4 cathodes to RV coil (ex. D1-RV, M2-RV, M3-RV and P4-RV) by attaching surface ECG cables (5 lead) to the patient through the programmer.
2. In the temporary settings, set the EGM to display lead II and LV tip-can.
3. Obtain an LV sensed event by disabling pacing and take a snap shot.
4. Change the sweep speed to 200mm/s and activate the calipers to measure the LV lead electrical delay as the interval from the earliest onset of the QRS from the surface ECG (any limb lead) to the first large positive or negative peak of the LV EGM during a cardiac cycle with the resolution of 5 ms.
5. Print and record this measurement and continue for each of the 4 cathodes. **During pre-discharge, we are capturing this information for data collection purposes only. Please do not choose a pacing vector with this information. Continue to utilize the pacing vector that was chosen at implant.**

For both groups, a device follow-up and interrogation will be done. Complete “RV Pace – LV Sense” conduction measurements (Appendix E). **During pre-discharge, we are capturing this information for data collection purposes only. Please do not choose a pacing vector with this information. Continue to utilize the pacing vector that was chosen at implant.**

Note: For both groups, the final programmed pacing vector should be the same vector that was chosen at implant.

- The following electrical measurements for the final programmed LV pacing vector will be performed:
 - Capture threshold testing using a 0.5ms pulse width. Lead impedance.

A Follow-up Case Report Form should be completed. If an adverse event has occurred since the last visit, an Adverse Event Case Report Form should be completed. If an adverse event occurs between scheduled visits, the event should be reported at the next scheduled visit. All forms should be submitted electronically to St. Jude Medical, using the EDC system.

A printout demonstrating the QLV measurement via the programmer for all 4 cathodes of the LV lead (QLV randomized patients only) will be submitted to SJM.

Export the device session records after all required testing has been performed, and submit to SJM using the EDC system. The device session records will include:

1. Initial and Final Programmed Parameters
2. Real-Time Measurements and Trends for all implanted leads
3. Capture threshold testing for the LV lead
4. All “new” stored EGM(s) since previous session
5. RV pace –LV sense conduction measurements

3.5.2 3 month Visit

For patients that are randomized to the QLV based implant strategy, QLV measurements will be completed with the programmer

1. During device follow up, gather a QLV measurement for each of the 4 cathodes to RV coil (ex. D1-RV, M2-RV, M3-RV and P4-RV) by attaching surface ECG cables (5 lead) to the patient through the programmer.
2. In the temporary settings, set the EGM to display lead II and LV tip-can.
3. Obtain an LV sensed event by disabling pacing and take a snap shot.
4. Change the sweep speed to 200mm/s and activate the calipers to measure the LV lead electrical delay as the interval from the earliest onset of the QRS from the surface ECG (any limb lead) to the first large positive or negative peak of the LV EGM during a cardiac cycle with the resolution of 5 ms.
5. Print and record this measurement and continue for each of the 4 cathodes. Once all 4 measurements have been obtained, choose a vector that corresponds to the cathode with the longest QLV.

For all patients, a device follow-up and interrogation will be done.

- Complete “RV Pace – LV Sense” conduction measurements (Appendix E). **During the 3 month visit, we are capturing this information for data collection purposes only. Please do not choose a pacing vector with this information.**

Note: For both groups, final programming of the LV lead configuration and device parameters is physician preference.

- The following electrical measurements for the final programmed LV pacing vector will be performed:
 - Capture threshold testing using a 0.5ms pulse width.
 - Lead impedance.

A Follow-up Case Report Form should be completed. If an adverse event has occurred since the last visit, an Adverse Event Case Report Form should be completed. If an adverse event occurs between scheduled visits, the event should be reported at the next scheduled visit. All forms should be submitted electronically to St. Jude Medical, using the EDC system.

A printout demonstrating the QLV measurement via the programmer for all 4 cathodes of the LV lead (QLV randomized patients only) will be submitted to SJM.

Export the device session records after all required testing has been performed, and submit to SJM using the EDC system. The device session records will include:

1. Initial and Final Programmed Parameters
2. Real-Time Measurements and Trends for all implanted leads
3. Capture threshold testing for the LV lead
4. All “new” stored EGM(s) since previous session
5. RV pace –LV sense conduction measurements

3.5.3 6 Month and 12 Month visit

For patients that are randomized to the QLV based implant strategy, QLV measurements will be completed with the programmer

1. During device follow up, gather a QLV measurement for each of the 4 cathodes to RV coil (ex. D1-RV, M2-RV, M3-RV and P4-RV) by attaching surface ECG cables (5 lead) to the patient through the programmer.
2. In the temporary settings, set the EGM to display lead II and LV tip-can.
3. Obtain an LV sensed event by disabling pacing and take a snap shot.
4. Change the sweep speed to 200mm/s and activate the calipers to measure the LV lead electrical delay as the interval from the earliest onset of the QRS from the surface ECG (any limb lead) to the first large positive or negative peak of the LV EGM during a cardiac cycle with the resolution of 5 ms.
5. Print and record this measurement and continue for each of the 4 cathodes. Once all 4 measurements have been

obtained, choose a vector that corresponds to the cathode with the longest QLV.

For all patients, a device follow-up and interrogation will be done.

- Complete “RV Pace – LV Sense” conduction measurements (Appendix E). **We are capturing this information for data collection purposes only. Final vector selection should not be made with this information.**

Note: For both groups, final programming of the LV lead configuration and device parameters is physician preference.

- The following electrical measurements for the final programmed LV pacing vector will be performed:
 - Capture threshold testing using a 0.5ms pulse width. Lead impedance.

In addition, the following information will be collected at the 6 and 12 month visits: NYHA classification, MLWHF QOL survey and patient global assessment (Appendix E). See Appendices A, B and E for instructions. A 2D echocardiogram will also be performed. The NYHA classification and patient global assessment may be performed by an experienced cardiologist blinded to the patient’s randomization assignment.

A Follow-up, Echo, Minnesota Living with Heart Failure, and Patient Global Assessment Case Report Form should be completed. If the patient experienced adverse event(s) or protocol deviation, complete an Adverse Event and/or Deviation Case Report Form(s). All forms should be submitted electronically to St. Jude Medical, using the EDC system.

Export the device session records after all required testing has been performed, and submit to SJM using the EDC system. The device session records will include:

1. Initial and Final Programmed Parameters
2. Real-Time Measurements and Trends for all implanted leads
3. Capture threshold testing for the LV lead
4. All “new” stored EGM(s) since previous session
5. RV pace-LV sense conduction measurements

3.5.4 System Revisions

For all system/lead revisions, complete the applicable testing as outlined in section 3.4.3.3. If the LV lead is replaced and the patient was previously randomized to the QLV based implant strategy, then an

attempt should be made to place the LV lead in the vein that previously showed the longest QLV measurement at initial implant and the EP system shall be used to measure the QLV for each of the four cathodes and programmed accordingly. Any explanted devices or leads (including damaged leads, lead segments, and lead fragments) should be returned to St. Jude Medical for analysis promptly. Any changes to the status of the lead (e.g. implanted, capped, removed) will be documented on the Product Out of Service Case Report Form. An Adverse Event, System Revision, Healthcare Utilization/Hospitalization and Out of Service (if applicable) Case Report Form(s) should be completed and submitted electronically to St. Jude Medical, using the EDC system.

All Case Report Forms should be submitted within 10 working days of applicable event (e.g., follow-up visit).

3.5.5 Product Out of Service

Complete the Product Out of Service Case Report Form if any implanted product is no longer in service (e.g. explanted or capped.)

4.0 Protocol Deviations

Investigators are required to adhere to the study protocol, signed Investigator's Agreement, applicable federal (national) or state/local, laws and regulations, and any conditions required by the IRB or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the clinical protocol was not followed. All deviations from the study protocol must be reported to St. Jude Medical as soon as possible, but no later than 10 working days of notification of the event. In addition, all deviations must be reported to the reviewing IRB per the IRB's reporting requirements.

Should a deviation occur, complete a Deviation Case Report Form and submit electronically to St. Jude Medical, using the EDC system. If a deviation occurs between scheduled visits, the event should be reported at the next scheduled visit. A Deviation Case Report Form will only be needed for scheduled visits, not unscheduled.

5.0 Adverse Events

Adverse events are any unfavorable clinical event which impacts, or has the potential to impact the health or safety of a patient caused by or associated with a study device or intervention. Adverse events will be classified as complication or observations.

Complications: Adverse events that require invasive intervention (e.g. lead dislodgement requiring repositioning).

Observations: Adverse events that can be managed without invasive intervention (e.g., oversensing or loss of pacing capture, which is remedied by reprogramming of the pulse generator).

Potential Adverse events associated with the use of left ventricular leads include:

- Allergic reaction to contrast media
- AV nodal reentrant tachycardia
- Body rejection phenomena
- Cardiac/coronary sinus dissection
- Cardiac/coronary sinus perforation
- Cardiac tamponade
- Coronary sinus or cardiac vein thrombosis
- Death
- Endocarditis
- Excessive bleeding
- Hematoma/seroma
- Induced atrial or ventricular arrhythmias
- Infection
- Lead dislodgement
- Lead/port damage
- Local tissue reaction; formation of fibrotic tissues
- Loss of pacing and/or sensing due to dislodgement or mechanical malfunction of the pacing lead
- Myocardial irritability
- Myopotential sensing
- Pectoral/diaphragmatic/phrenic nerve stimulation
- Pericardial effusion
- Pericardial rub
- Pneumothorax/hemothorax
- Prolonged exposure to fluoroscopic radiation
- Pulmonary edema
- Renal failure from contrast media used to visualize coronary veins
- Rise in threshold and exit block
- Thrombolytic or air embolism
- Valve damage

Performance of a coronary sinus venogram is unique for lead placement in the cardiac venous system, and carries risks.

Potential complications reported with direct subclavian venipuncture include hemothorax, laceration of the subclavian artery, arteriovenous fistula, neural



damage, thoracic duct injury, cannulation of other vessels, massive hemorrhage, and rarely, death.

Potential Adverse Events associated with the system, but are not limited to the following:

- Acceleration of arrhythmias (caused by device)
- Air embolism
- Allergic reaction
- Bleeding
- Cardiac tamponade
- Chronic nerve damage
- Death
- Erosion
- Exacerbation of heart failure
- Excessive fibrotic tissue growth
- Extracardiac stimulation (Phrenic nerve, diaphragm, chest wall)
- Extrusion
- Fluid accumulation
- Formation of hematomas or cysts
- Inappropriate shocks
- Infection
- Keloid formation
- Lead abrasion and discontinuity
- Lead migration/ dislodgement
- Myocardial damage
- Pneumothorax
- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Potential mortality due to inability to defibrillate or pace
- Thromboemboli
- Venous occlusion
- Venous or cardiac perforation

Patients susceptible to frequent shocks despite antiarrhythmic medical management may develop psychological intolerance to a CRT-D system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking (phantom shock)



Should an adverse event occur, complete and submit an Adverse Event form to St. Jude Medical using the EDC system. Report the adverse event to the IRB per the IRB policy. Return any explanted devices or leads to St. Jude Medical for analysis.

For other events not listed the site should follow their standard reporting practices for medical device reporting per 21 CFR 803.

6.0 Other Reported Events

An Other Reported Event is any other clinical event that is submitted by the investigator which is not caused by or associated with the study device and/or system component(s) and/or defined as an Adverse Event in section 5.0.

7.0 Healthcare Utilization/Hospitalization Visits

In-patient, ER, observational, urgent care or outpatient visits for all causes must be reported using the Healthcare Utilization/Hospitalization Case Report Form.

A Healthcare Utilization/Hospitalization Case Report Form should be completed for unscheduled office visits where device interrogation and reprogramming associated with the Quartet LV lead OR administration of IV diuretics, inotropes, and/or vasodilators takes place. A Healthcare Utilization/Hospitalization Case Report Form should not be completed for office visits that are part of a required study visit (described in section 3.5)

The Healthcare Utilization/Hospitalization Case Report Form should be submitted to St. Jude Medical using the EDC system.

A CEC will review and adjudicate all HF hospitalizations. The CEC will base their final adjudication on the information provided on the case report forms, medical records, and their clinical knowledge and experience.

8.0 Deaths

All patient deaths that occur during this study must be reported to St. Jude Medical within 10 working days of the center being notified. Notification of death should include a detailed statement of the pertinent events and be signed by the investigator in addition to the appropriate case report forms (Patient Death form, Withdrawal form, and Product Out of Service form). A Mortality Committee will review and classify all patient deaths. It is the investigator's responsibility to notify the IRB per the IRB policy. Details of death and the following information, if available, should be provided in a letter to St. Jude Medical by the investigator summarizing the patient's course since enrollment in the study:

- Date and time of death
- Place death occurred (e.g. hospital, nursing home, patient's home)
- If death was witnessed
- Identification of the rhythm at the time of death, if known (include any available documentation)
- Cause of death
- Any other circumstances surrounding the death
- Approximate time interval to death from the initiating event.
- Autopsy report (if performed)
- Whether it was device and/or procedure-related
- Whether it was related to the study
- Device configuration at the time of death

Provide clinical notes and witness statements. If possible, interrogate the pulse generator. Retrieve and print all episode diagnostics, EGMs, and programmed parameters. If applicable, the pulse generator should then be programmed OFF.

Every attempt should be made to explant the pulse generator and/or leads intact. Any explanted devices or leads should be returned to St. Jude Medical for analysis promptly. In the event that the device is not explanted, the above procedure must be followed to retrieve the data. The reason the pulse generator and/or lead(s) are not being returned to St. Jude Medical must be stated clearly on the Case Report Form.

9.0 Withdrawals

Withdrawal is defined as termination of participation of a patient from a clinical trial. All reasonable efforts should be made to retain the subject in the clinical trial until completion of the clinical trial. Reasons for withdrawal include, but are not limited to the following:

- Heart transplant
- Patient Lost to Follow-ups- Defined as the following: A patient is considered lost to follow up when reasonable efforts to contact the patient

have been exhausted and study personnel have abandoned such efforts. Reasonable effort is defined as a minimum of two documented phone calls made by personnel at the study center to the patient or emergency contact and a certified letter was sent to the last known address, and two consecutive visits pass without contact from or with the patient.

- Unsuccessful implant
- Patient deaths
- Patient participation terminated by investigator
- Patient and/or family request
- System explanted without a System Replacement
- Sponsor request

Please complete a Withdrawal Case Report Form and record all results. If the patient experienced an adverse event or protocol deviation, complete an Adverse Event and/or Deviation Case Report Form. Submit the forms electronically to St. Jude Medical, using the EDC system.

10.0 Risks and Benefits

10.1 Risks

The risks associated with the use of the Quadripolar CRT-D device system in a CRT-D indicated patient population with advanced heart failure are anticipated to be comparable to those associated with the use of other SJM legally marketed CRT-D devices and leads. Patients participating in this study are clinically indicated for a CRT-D system as part of their medical management and are subject to the risks associated with an implant procedure (refer to Section 5.0).

10.2 Benefits

There are no direct benefits to the patient as a result of their participation in this study. All patients may be more closely monitored by their physician. We hope the information learned from this pilot study will benefit patients diagnosed with heart failure in the future and assist physicians with decreasing the number of CRT nonresponders.

11.0 Investigator Information

This study protocol will be conducted by investigators with experience and/or willingness to be trained in the use of CRT-D devices. A principal investigator should have experience in and/or will be responsible for:



- Conducting the study protocol in accordance with the signed agreement with St. Jude Medical, the study protocol, all applicable FDA regulations (21 CFR Parts 50, 54, 56, 812), GCP guidelines, and any conditions of approval imposed by the IRB
- Providing signed Investigator/Co-Investigator (s) Agreement
- Providing IRB Approved Informed Consent
- Collection and archiving of data obtained pursuant to the requirements of the study protocol during the course of the study and after the study has been completed
- Screening and selecting appropriate patients

It is acceptable for the principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the study protocol, complying with the study protocol and collecting all required data.

12.0 Monitoring Procedures

St. Jude Medical will serve as the “sponsor” of the ENHANCE CRT study. It is the responsibility of St. Jude Medical as the “sponsor” of the study to ensure proper monitoring of the study and to see that all the clinical requirements are met.

A St. Jude Medical monitor may visit the investigator or designee periodically during the study to monitor progress, assist in gathering the required data, verify study endpoints, clarify data discrepancies, and to answer any questions. During these visits, the clinical monitor will review the patient’s records to verify that all records and files are up to date, and to assure compliance with all requirements of the protocol and local IRB procedures. A monitoring report following the on-site visit will be provided to the site to document monitoring findings.

The investigator will make patient and study records available to the clinical monitor for periodic inspection.

Responsibility for overall study management will be held by the Director of Clinical Affairs, St. Jude Medical, IESD.

Clinical Studies Department
St. Jude Medical IESD
15900 Valley View Court
Sylmar, CA 91342
TEL: (800) 423-5611 ext. 2608
FAX: (800) 254-6411

FDA Inspections

The investigator and /or designee should contact St. Jude Medical within 24 hours upon being notified of an impending FDA inspection. A clinical monitor may assist and review study documentation with the investigator and/or designee to prepare for the audit.

An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

13.0 Consent Materials

A proposed informed consent is attached in Appendix F. Failure to obtain informed consent from a patient prior to study enrollment should be reported to St. Jude Medical as soon as possible, but not later than 10 working days via a protocol deviation form, and to the reviewing IRB consistent with the IRB's reporting requirements.

14.0 IRB Information

IRB approval for the study and informed consent will be required prior to beginning the study. A copy of the IRB approval and corresponding informed consent must be forwarded to St. Jude Medical prior to authorization of the institution to begin the study. Any withdrawal of IRB approval should be reported to St. Jude Medical as soon as possible.

15.0 Records Retention Period

Clinical investigators of St. Jude Medical studies are required to maintain records during the study and for a period of two years after the date on which the study is terminated or completed.

16.0 Publication

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

APPENDIX A**NYHA CLASS ASSESSMENT**

To assess patients NYHA class follow standard guidelines:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX B

QUALITY OF LIFE (QOL) QUESTIONNAIRE GUIDELINES

MINNESOTA LIVING WITH HEART FAILURE (MLHF) QUESTIONNAIRE GUIDELINES FOR ADMINISTRATORS

The questionnaire should be administered before the patient is seen by his/her physician.

Give target respondents a questionnaire when they check in for their appointment. The following script (or a variation appropriately reworded to sound more like your style of speech) is suggested for introducing the MLHF:

We would like to better understand how you and other persons in this study feel, how well you are able to do your usual activities, and how you rate your own health. To help us better understand these things about you and other persons, please complete this questionnaire about your general health.

*The questionnaire is simple to fill out. Be sure to read the instructions on the top of the first page [point to them]. Remember, this is not a test and there are no correct or wrong answers. Choose the response that best represents the way **you** feel. I will quickly review the questionnaire when you are done to make sure that all the items have been completed.*

*You should answer these questions by yourself. Spouses, or other family members, or visitors, **should not** assist you in completing the questionnaire.*

Please fill out the questionnaire now. I will be nearby in case you want to ask me any questions. Return the questionnaire to me when you have completed it.

Administering and Completing the MLHF

Provide a firm writing surface such as a clipboard or table top and a pen to the patient to complete the form.

When the respondent returns the MLHF, check the questionnaire for completeness. Note whether the questionnaire is complete. If it is not complete, ask the respondent whether he/she had any difficulty completing it and record the reasons for non-completion.

QUESTIONNAIRE ADMINISTRATION DO's AND DON'Ts

DO's	DON'T'S
Do have the respondents fill out the questionnaire before they fill out any other health data forms and before they see their physicians	Do not discuss respondents' health, health data, or emotions with them before they fill out the questionnaire
Do be warm, friendly, and helpful	Do not force or command respondents to fill out the questionnaire
Do request and encourage respondents to fill out the questionnaire	Do not accept an incomplete questionnaire without first encouraging the respondent to fill out unanswered questions
Do read and repeat a question verbatim for the respondent	Do not interpret or explain a question
Do tell respondents to answer a question based on what they think the question means	Do not force or command respondents to fill out a particular question
Do have respondents fill out the questionnaire by themselves	Do not allow spouses or family members to help the respondent fill out the questionnaire
Do encourage respondents to fill out all questions	Do not minimize the importance of the questionnaire
Do thank respondents for filling out the questionnaire	
Do inform respondents if they will be asked to fill out the same questionnaire again at other clinic visits	

Let the patient know that he/she will be asked to complete the questionnaire again at a later date.

Be sure to put the completed questionnaire in a safe and secure place to ensure confidentiality.

Addressing Problems and Questions

What should I do if the respondent refuses to fill out the MLHF? Respondents are not required to fill out the questionnaire. If the respondent is able to self-administer the MLHF but *refuses* to participate, tell the respondent that completion of the questionnaire is voluntary, but that it will provide helpful health-related information. In clinical settings, this will help their physician better understand their health problems.

Emphasize that these data are as important as any of the other medical information. The questionnaire responses are essential in order to get a complete picture of the respondent's health. Emphasize that the questionnaire is simple to fill out. Suggest that it is possible that this questionnaire is different from others they have filled out in the past, and that they may

even enjoy filling out this questionnaire. If the respondent still refuses, take back the questionnaire, record the reason for refusal, and thank the respondent.

What if a respondent does not complete the MLHF? If non completion is a result of the respondent having trouble understanding particular items, ask the respondent to explain why they had difficulty responding to those items. Reread the question for them verbatim, but do not rephrase the question. If the respondent is still unable to complete the survey, accept the survey as incomplete, and indicate that the respondent was unable to complete the survey due to difficulty understanding questions. If the respondent is unable to self-administer the questionnaire, document the reason. If the reason is health related, indicate the specific reason.

What should I do if the respondent asks for clarification of an item? While completing the questionnaire, some respondents might ask for clarification of *specific items* so that they can better understand and respond to a question. If this happens, the staff member can assist the respondent by rereading the question for them verbatim. If the respondent asks what something means, do not try to explain what the question means, but suggest that the respondent use his or her own interpretation of the question. All respondents should answer the questions based on what they think the questions mean.

Sometimes respondents may have trouble with the response choices. They may say “I don’t know” or something different than what is stated on the questionnaire. In these circumstances it is important to gently guide the respondent to respond in one of the pre-set categories by saying something like:

I know that it may be hard for you to think this way, but which of these categories most closely expresses what you are thinking or feeling?

It is possible that respondents may ask if certain items, particularly the pain items, are limited to a specific health problem. Explain to the respondent that these questions ask about their health in general.

If the respondent does not like a question, or thinks it is unnecessary or inappropriate, emphasize that all questions are in the survey for a reason that is very important to the study. They should try to answer all of the questions.

Differences in answers due to different wordings of the questionnaire can bias results. It is important to minimize these differences. If the respondent has repeated difficulties filling out the questionnaire which you cannot address with the above direction, thank the respondent, take back the questionnaire, and record the difficulty.

What should I do if a respondent wants to know what his/her answers mean? If a respondent asks for interpretation of their responses or asks for their score on the questionnaire, tell respondents that you are not trained in how to score or interpret the questionnaire. Emphasize that their answers are to be kept confidential.

What should I do if a respondent is concerned someone will see their answers? Emphasize that all respondents' responses to the MLHF are to be kept confidential. You are not allowed to read the responses other than to check that all responses are answered. If an ID number is used to identify a respondent, point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. If this is for a clinical study, tell respondents that their answers to the questionnaire will be pooled with other respondents' answers and that they will be analyzed as a group rather than as individuals for the study.

What should I do if a respondent asks why the MLHF must be filled out more than once? Explain that respondents must fill out the same questionnaire at additional visits in order to see if their answers change over time. This will give a more complete picture of the respondent's health over the course of time.

APPENDIX C

QLV MEASUREMENT INSTRUCTIONS AT IMPLANT

Set Up:

1. Before the patient is draped and prepped for the procedure, confirm that surface ECG cables are correctly placed on the patient and connected to the EP recording system (GE Cardiolab, Prucka, SJM EP Workmate, etc.). Display the limb lead (I, II, III, aVR, aVL or aVF) that shows the earliest onset of QRS on the recording system.
2. Prepare connections used for the QLV measurements (RV and LV leads) via the EP recording system.
 - a. Identify which ports on the EP connector block will be used to record RV and LV IEGM signals and label accordingly in the EP system application BEFORE the case starts.
 - b. Be sure to display the RV/LV IEGMs during QLV measurements.
3. Provide cables and accessories required for lead testing and QLV measurements:
 - a. PSA testing cable(s) for standard lead testing
 - b. TWO sterile threshold testing cables (SJM CVD Product# 401748) which will be referenced as the “EP Testing Cables” to record RV/LV signals via the EP recording system.



- c. DF-4/IS-4 connector sleeve (SJM CRM Product# EX3151) which will be referenced as the “IS-4 Connector Sleeve”

**LV lead placement in non-traditional vessel (inclusive of the anterior region):**

4. When placing the LV lead, attempt a non-traditional vessel (inclusive of the anterior region) for the first LV lead position. (Note: A non-traditional vessel (inclusive of the anterior region) will be tested first and a traditional free lateral branch will be tested second.)
5. Once the LV lead is placed, perform “standard of care” PSA measurements (capture threshold, lead impedance, etc.) in the desired vector.
6. Once acceptable LV lead placement is obtained in the first (non-traditional) branch, disconnect the PSA testing cables from the LV lead.

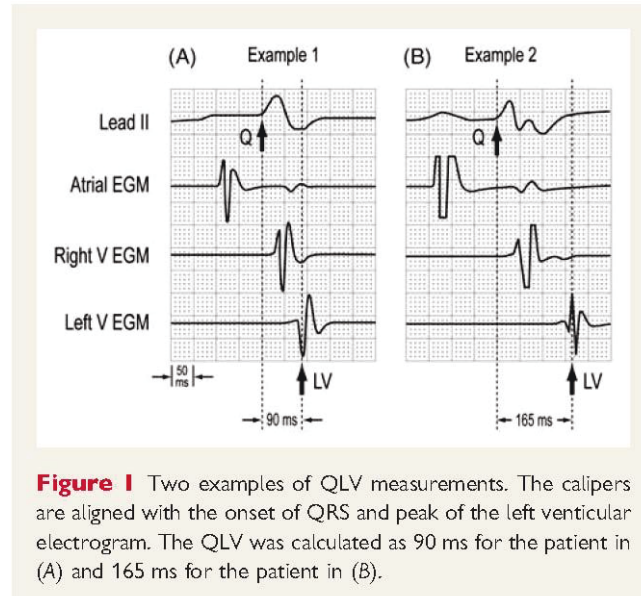
Recording snapshots for QLV measurements:

7. Record snapshots for QLV measurements for each LV electrode (D1, M2, M3, and P4) as described below. Set the high-pass filter to 30 Hz and the low-pass filter to 500 Hz in the EP recording system application. The recording via the EP system should begin at this point, if not already recording.
 - a. Connect the pin connectors of both EP Testing Cables to the EP system connector block (in the ports designated for the RV and LV IEGMs).
 - b. Connect the alligator clips of one EP Testing Cable to the LV lead in a UNIPOLAR configuration.
 - i. Attach the red alligator clip to the patient’s subcutaneous tissue in the pocket or close to it. The red alligator clip should not be clipped to the outer skin.
 - ii. Place the black alligator clip on the IS-4 Connector Sleeve for the LV electrode (e.g. D1) being tested.
 - c. Confirm that the LV IEGM is displayed on the EP system (eliminate any noise or artifacts from the signal). If there is excessive noise on the signals, please reconnect the red alligator clip to another location on the patient’s subcutaneous tissue. The electrode should not be clipped to the outer skin.
 - d. Connect the alligator clips of the second EP Testing Cable to the RV lead in a BIPOLAR configuration.
 - e. Confirm that the RV bipolar IEGM is displayed on the EP system.
 - f. Via the EP monitoring system, record/store snapshots (at least 5 seconds long) for the LV cathode being tested, ensuring that the surface ECG, RV IEGM, and LV IEGM are displayed. Use the Event or Notes feature to annotate the recording/snapshot, including the

specific branch where the LV lead is positioned and which LV cathode (e.g. D1) is being tested.

Record the following at each LV cathode:

- i. Non-paced for the QLV and RV Sense to LV sense measurements.
- ii. RV paced for the RV paced to LV sense measurement.
- g. Pace at 10V output to assess if phrenic nerve stimulation occurs when pacing from the LV cathode being tested. Note any phrenic nerve stimulation that may occur.
- h. Repeat steps a-f for the other LV cathodes (e.g. M2, M3, and P4).
- i. Measure the QLV, RVsense to LV sense, and RV pace to LV sense from the stored snapshots of each of the LV cathodes (e.g. D1, M2, M3, P4) in the non-traditional branch while the implanter repositions the LV lead in a traditional free lateral branch:
 - i. Change the sweep speed of the snapshot to 200mm/s.
 - ii. Activate the calipers to measure the LV lead electrical delay as the interval from the earliest onset of QRS (via any lead) of the surface ECG to the first large positive or negative peak of the LV IEGM during a cardiac cycle with the resolution of 5 ms. The amplitude of the first large peak needs to be > 50% of the amplitude of the largest peak in the same cardiac cycle. If necessary, adjust the gain to identify the “onset of QRS”. See the example of QLV measurement below¹⁴.



- iii. Print the snapshot with the calipers for every measurement.

LV lead placement in the traditional/lateral LV branch:

8. After the LV lead has been repositioned in the second (traditional/lateral) LV branch, repeat this procedure starting at step 5.

Assessment of QLV measurements for final LV lead placement:

9. Compare all QLV measurements for the non-traditional vessel (inclusive of the anterior region) versus the traditional/lateral branch to determine which branch yielded the longest QLV measurement.
 - a. Target the corresponding branch (non-traditional vessel (inclusive of the anterior region) or traditional/lateral) for final LV lead placement.
 - b. If the lead is moved back to the non-traditional vessel (inclusive of the anterior region), repeat QLV measurements (7a through 7k) corresponding to the final LV lead position.

Cathode selection for LV pacing configuration:

10. Once the final LV lead placement has been established, the vector should be programmed to include the LV electrode (cathode) that resulted in the longest QLV (e.g. if D1 had the longest QLV, then permanently program either D1-M2, D1-P4, or D1- RV Coil as the final vector).

(Note: If there are multiple cathodes with relatively long QLV measurements, then the cathode with the longest QLV should be chosen. If that cathode has signs of positive phrenic nerve stimulation, then choose the cathode that gives the second longest QLV. Continue until a cathode that does not have signs of phrenic nerve stimulation is identified and permanently programmed.)
11. Record LV impedance and capture threshold at 0.5ms with this programmed vector and print and record the results.
12. If the final LV lead location is in the apical region, then the RV lead could be re-positioned (at the discretion of the implanting physician) to the mid-ventricular or high septal region.

Exporting data from the EP system:

13. At the end of the study, export data from EP system to a USB drive.
 - a. If using EP-WorkMate, end the present study. Ensure the USB drive is plugged in. From the main menu, select Archive Signals. Check the study patient with the QLV measurements. Check the box for Archive Path corresponding to the DVD drive. **Important: Make sure the “Remove from Hard Drive after Archive” box is not checked.** Push Archive button.
 - b. If using GE CardioLab (also known as Prucka), print a copy of the log at the end of the study. This hard copy needs to be provided along with the data. Ensure the USB drive is plugged in. From the Measurements menu, choose Data Extraction. Select Text mode, and choose only the pages for extraction that contain the LV IEGMs, the RV IEGMs and the ECG signals. To pick the start and stop time, click in the log window on the events at the start and stop of the first QLV snapshot. If necessary, select the path to the USB drive. Press the Extract button to save the data. For each additional QLV snapshot, repeat the data extraction.

APPENDIX D

PATIENT GLOBAL ASSESSMENT

The patient will rate their condition with regard to their heart failure by answering the following question on the CRF:

“Specifically in reference to your heart failure symptoms, how do you feel today as compared to how you felt before having your CRT-D system implanted?”

The response will be provided by checking one of the following options on the CRF:

- 1) Markedly improved
- 2) Moderately improved
- 3) Slightly improved
- 4) No change
- 5) Slightly worse
- 6) Moderately worse
- 7) Markedly worse

APPENDIX E

Instructions for running the RV pace-LV sense Conduction Measurement for ENHANCE CRT

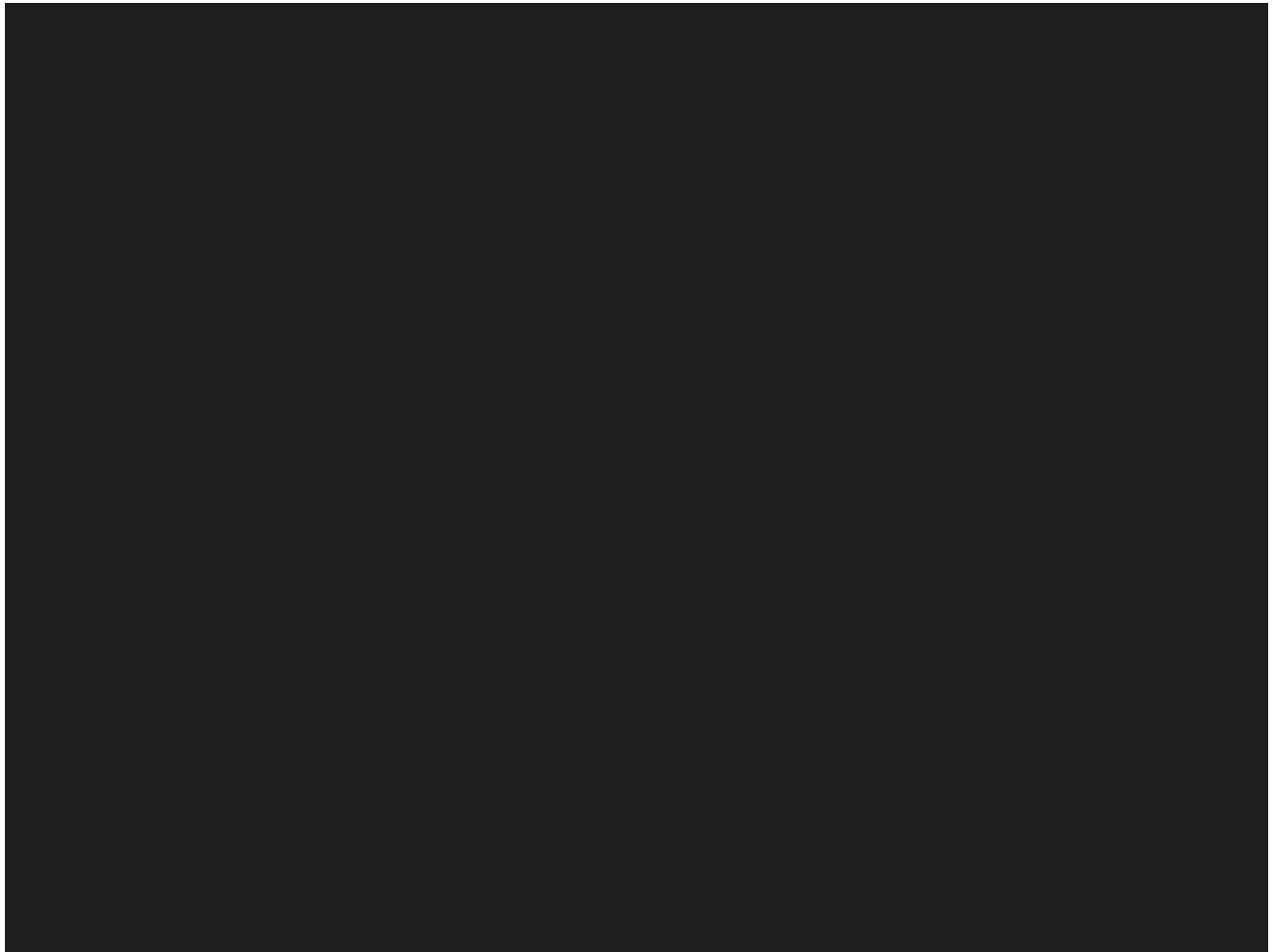
Because the ENHANCE CRT patients are all non-LBBB patients, it is recommended that the RV-LV conduction measurement is run using “RV Pace” Test Method.

- 1) Navigate to **Tests**→**CRT Toolkit**. Next to **RV-LV Conduction Time**, click on the blue **Perform Measurements** button.





2) The following screen will pop up. Click on the additional parameters box.



- 3) Click on **RV Sense** to change it to **RV Pace**.





- 4) Double-check that the remaining parameters will ensure pacing in the RV by clicking on **Start Temporary**, then click the **X** to return to the previous screen.

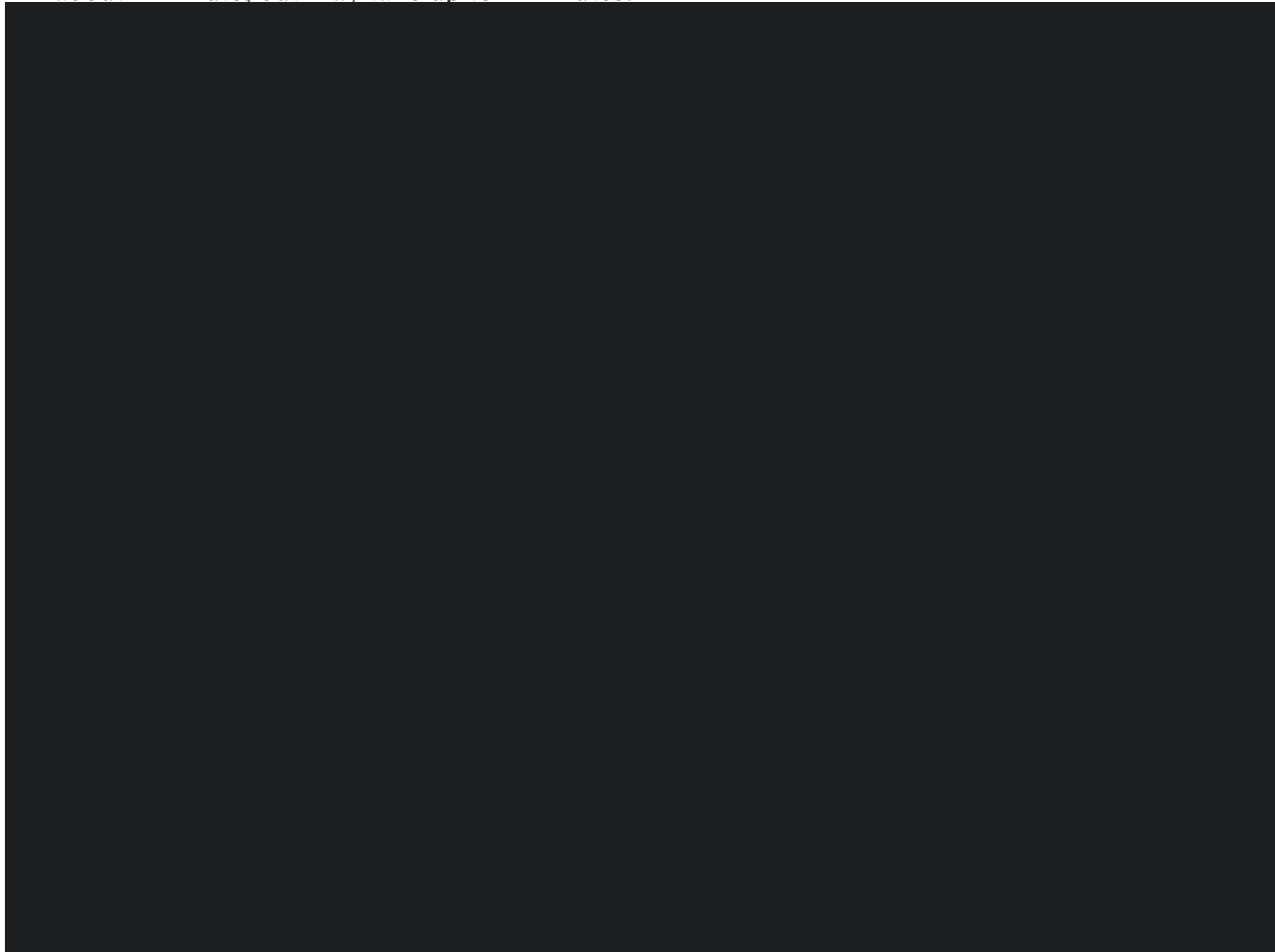


- 5) Click on the green **Perform Measurements** button to initiate the measurements.



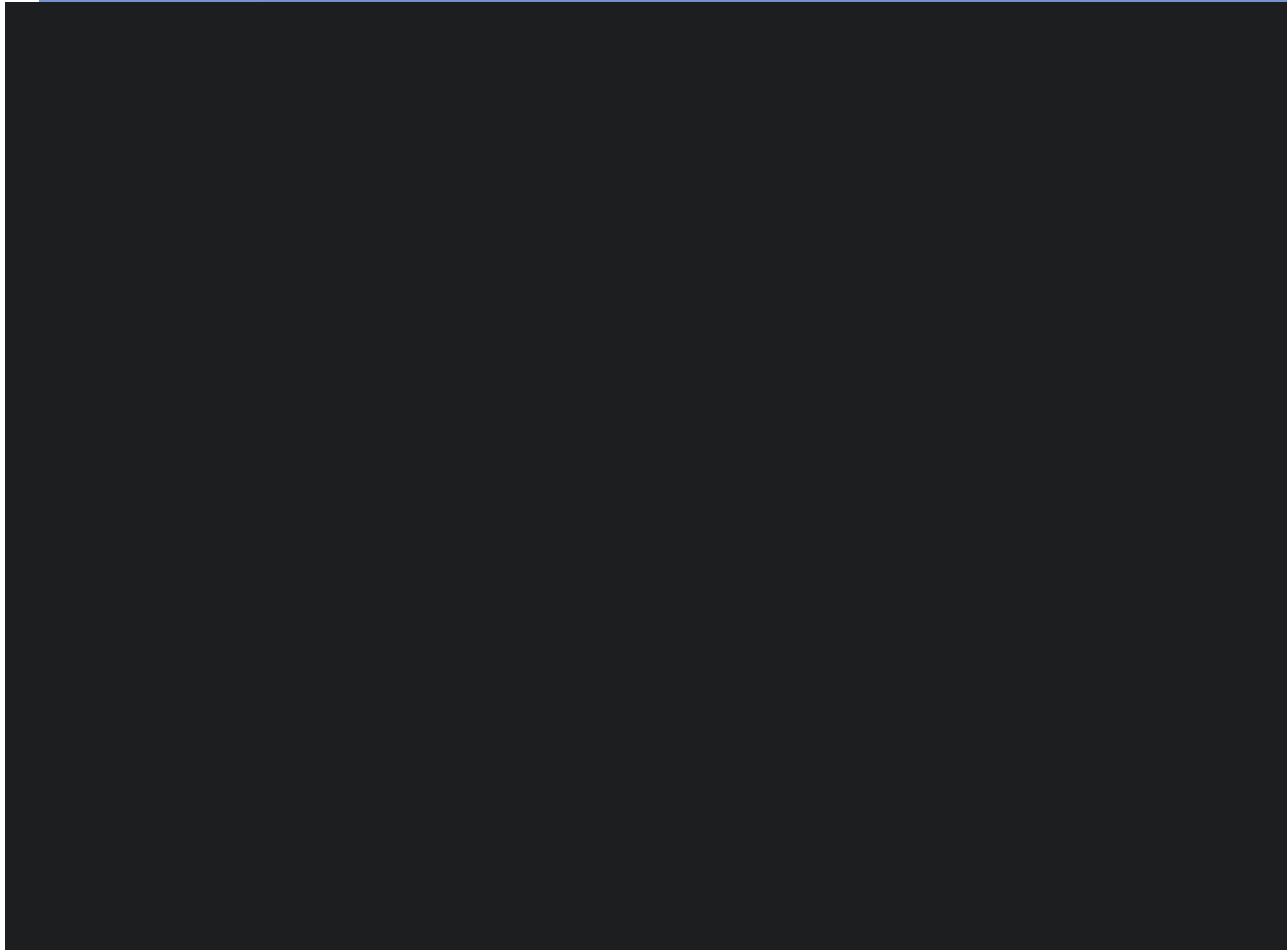


- 6) The measurements will proceed automatically. The process will probably take about 1 minute, but may take up to 2 minutes:





- 7) Upon completion, the RV-LV conduction time for all four electrodes will be reported as shown below. They will also be available on the printed CRT Toolkit Report if it is printed at the end of the follow-up.



APPENDIX F

Statement of Informed Consent

Study Title: CRT IMPLANT STRATEGY USING THE LONGEST ELECTRICAL DELAY FOR NON-LEFT BUNDLE BRANCH BLOCK PATIENTS (ENHANCE CRT)

Introduction

You are being asked to participate in the ENHANCE CRT study, a prospective, randomized, double-blinded postmarket study. This study involves research. This informed consent explains why this study is being performed and what your role will be if you decide to participate. This study is sponsored by St. Jude Medical. This company currently manufactures Cardiac Resynchronization Therapy Defibrillators (CRT-Ds), Implantable Cardiac Defibrillators (ICDs), pacemakers, lead systems, heart valves and catheters.

Please read this form and feel free to ask your doctor any questions you may have about the information provided. You will be given the opportunity to ask questions and have your questions answered before making a decision whether to take part in the study. Please take your time and discuss this information with your family, friends or family physician.

If you agree to be in the study, you will need to sign this consent form. You will be given a copy of this signed consent form to keep. Your participation is entirely voluntary and you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled.

What is the purpose of this study?

Your doctor has determined that you may benefit from Cardiac Resynchronization Therapy (CRT) to treat and lessen the symptoms related to your heart failure (HF). Cardiac resynchronization is a therapy that stimulates both the right and left side of the heart to improve the heart's ability to pump. This pacing of both sides of your heart is done via a CRT-D device and 3 wires that are inserted into your heart. The third wire (LV lead) will be positioned in a location on the lower left chamber of the heart known as the left ventricle. On this wire, there are 4 cathodes that can pace your heart. These electrodes can be tested and programmed by your doctor in 10 different ways. The purpose of this study is to determine which of the 4 cathodes and which of the two veins in your heart decrease heart failure symptoms the most.

During this study, patients will be divided into two groups. If you agree to participate in this study, you will be randomized (chosen like a flip of a coin) to be put in one of the two groups. These two groups will differ in the way your physician will choose the location for the left ventricle wire (LV lead) and selection of the site for pacing. In one group, the 4

cathodes of the LV lead will be tested in two different veins in the heart during implant. One vein runs on the front portion of the heart and the other vein runs down the side or back portion of the heart. In the other group, your doctor will implant the LV lead in their usual method (rely on the X-rays and his/her judgment for selecting the vein and the pacing site for your left ventricular lead).

You are being asked to participate because you are having a St. Jude Medical Quadripolar CRT-D system (CRT-D device and the Quartet LV lead) implanted. The St. Jude Medical Quadripolar CRT-D system is already approved by FDA.

Two hundred fifty (250) patients will be enrolled in this study. Patients will be enrolled at a maximum of 40 investigational centers located in the United States. All patients will be implanted with the Quadripolar CRT-D device system and participate in this study for approximately 12 months.

What will happen if I take part in this study?

If your doctor determines that you qualify, and you decide to take part in this study, the following procedure(s) will be performed.

During the enrollment visit, the following will be completed:

- A medical history will be taken.
- A healthcare provider will ask you questions about your heart failure symptoms. This study is a double-blinded study. This means that you and the doctor who is assessing you, will not know which group you are in. However, your study doctor will know which group you are in while caring for you.
- The study doctor or study staff will ask you about the medications that you take every day.
- You will be asked to complete a questionnaire on your daily activities (called the Minnesota Living with Heart Failure Questionnaire).
- An echocardiogram will be performed.

Patients will be randomized to one of the two groups prior to the implant procedure.

During the implant procedure, you will receive a CRT-D device and Quartet LV lead. The CRT-D device and Quartet LV lead will be implanted during a procedure in the Electrophysiology Laboratory (EP Lab) or in the Operating Room (OR). During the procedure, your CRT-D device will be tested using a programmer (computer) that will be used to communicate with your CRT-D system. For patients that are randomized (flip of a coin) to the group that will have the LV lead implanted in the physician's usual method, the implant procedure time will be the same as if you were receiving a CRT-D device and not participating in a study. The total estimated time for a CRT-D procedure and the additional testing is approximately 2 hours. For

patients that are randomized (flip of a coin) to the group that will have the 4 cathodes of the LV lead tested in two different veins in their heart during implant, the additional testing that will be completed for the purposes of the study will add approximately an additional 15 minutes to the implant procedure time. Venogram and fluoroscopy images (pictures of the veins of the heart before and after lead placement) are routinely taken during a CRT-D device implant procedure. Both patient groups will have these images taken during the implant procedure. These images will be sent to SJM.

Follow-up Requirements

If you decide to take part in this study, you will be required to return for follow-up visits. Both patient groups will have the same follow up schedule. The visits will be done at the following times:

- Pre-discharge (occurs prior to leaving the hospital)
- 3 months after implant at your doctor's office
- 6 months after implant at your doctor's office
- 12 months after implant at your doctor's office.

Pre-discharge visit:

- A chest X-ray will be performed to check the position of the lead (wire) in your heart. An X-ray technician will ask you to hold your breath for 5 seconds when the x-ray is taken. This procedure should take approximately 15 minutes.
- For both groups of patients, the CRT-D device will be tested using a programmer (computer) that will be used to communicate with your CRT-D system. You should not feel any discomfort during this procedure.
- For the patients that are randomized (flip of a coin) to the group that will have the four cathodes of the LV lead tested in two different veins in their heart during implant, device testing of the four cathodes will be performed at the follow up. This testing will add approximately 10 additional minutes to the follow up visit.

3 month visit:

- For both groups of patients, the CRT-D device will be tested using a programmer (computer) that will be used to communicate with your CRT-D system. You should not feel any discomfort during this procedure.
- For the patients that are randomized (flip of a coin) to the group that will have the four cathodes of the LV lead tested in two different veins in their heart during implant, device testing of the four cathodes will be performed at the follow up. This testing will add approximately 10 additional minutes to the follow up visit.

6 month and 12 month visit:

- For both groups of patients, the CRT-D device will be tested using a programmer (computer) that will be used to communicate with your CRT-D system. You should not feel any discomfort during this procedure.



- For the patients that are randomized (flip of a coin) to the group that will have the four cathodes of the LV lead tested in two different veins in their heart during implant, device testing of the four cathodes will be performed at the follow up. This testing will add approximately 10 additional minutes to the follow up visit.
- You will be asked to complete a questionnaire on your daily activities (called the Minnesota Living with Heart Failure Questionnaire).
- Your healthcare provider will ask you questions about your heart failure symptoms and assess the severity of those symptoms. This study is a double-blinded study. This means that you and the doctor who is assessing you, will not know which group you are in. However, your study doctor will know which group you are in while caring for you.
- An echocardiogram will be performed.

If you were hospitalized, admitted for an observational visit in the hospital, went to the Emergency Room or Urgent Care Center, or had an outpatient procedure during this study, please inform the treating doctor that you are taking part in this research study. If you have any changes in your address or telephone number over the length of this study, please report those changes to your doctor and to St. Jude Medical at (800) 423-5611 ext. 5802, or ask for Device Tracking.

What are the possible discomforts, side effects, and risks?

Since your CRT-D system and LV lead are all approved by the FDA, the risks associated with your participation will not be different than if you chose not to participate in this study.

An increase in the time it takes to perform the implant procedure may be observed. During the implant procedure, your vital signs such as blood pressure and heart rate, will be closely monitored. All non-essential testing will be stopped if it appears to jeopardize your health in any way. There should be no other additional risks to the patients enrolled in this study.

If you are pregnant or planning to become pregnant, you should discuss your participation with your study doctor. Patients who become pregnant while taking part in the study should contact the study doctor right away.

What are the possible benefits to you or to others?

There are no direct benefits to you as a result of your participation in this study. All patients may be more closely monitored by their physician. We hope the information learned from this study will benefit patients diagnosed with heart failure in the future and assist physicians with decreasing the number of patients who do not respond to CRT.

If you do not want to take part in this study, what other options are available to you?

If you choose not to be in the study, you will still receive a CRT-D implant and your doctor will still follow your progress in a similar manner.

How will your privacy and the confidentiality of your research records be protected?

If you choose to take part in this study, your medical records will be kept confidential to the extent provided by federal, state and local law. Nothing about you, your illness or your treatment will be made public. The information obtained from the study will be submitted to St. Jude Medical. The data will then be presented in a report to the applicable governmental agencies (for example: the Food and Drug Administration) or similar government agencies in other countries. The venogram and fluoroscopy images (pictures of the veins of the heart before and after lead placement) will be sent to a core lab in a de-identified format for interpretation and analysis. Your personal information will be kept confidential. Any publications using the information collected during the study will not include your name or any information that can identify you. Only information about your medical condition as it pertains to the study and the Quadripolar CRT-D device system will be provided to St. Jude Medical. In order to verify study data, monitors from governmental agencies (for example: the Food and Drug Administration), St. Jude Medical, and the hospital's Institutional Review Board/Ethics Committee will have the right to review your medical records as they pertain to this study. In addition, clinical trial information for such an investigation will be submitted for inclusion in the clinical trial registry databank.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

St. Jude Medical may export data to countries where different data protection laws apply.

If you receive medical care at another location while still being followed in this study, you agree to allow copies of your medical records from the location to be made available for collection of data related to the study.

If you choose to take part in this study, will it cost you anything?

No payment or compensation will be made to you for participation in this study. All test and procedures, as well as the cost of your CRT-D implantation will be the responsibility of you and your insurance company. There is no guarantee that your insurance company will cover 100% of the expenses. You are encouraged to check with your insurance company to verify coverage or payments of these procedures.

The testing and information collected at these follow up visits are no different than if you were not participating in this study.

Will you receive compensation for your participation in this study?

No payment or compensation will be made to you for your participation in this study.

What if the device needs to be removed?

If your CRT-D system or any part has to be removed, it will be returned to St. Jude Medical for analysis. In the event of your death, you agree that your implanted CRT-D system may be removed and returned to St. Jude Medical for analysis. Should you withdraw from this study and choose to have your CRT-D system or any part of it removed, the cost will be your responsibility.

Who can you contact for study information?

If you have any questions regarding your participation in this study, please contact Dr. _____ at ____ - ____ - ____.

In addition, if you have questions about your rights as a research patient, or if you have complaints, concerns, or questions about the research, please contact _____ the Institutional Review Board Administrator at ____ - ____ - ____.

What if you are injured because of the study?

In the event of injury to you resulting directly from your participation in this study, medical treatment shall be available to you. You or your insurance company shall be responsible for all costs as a result of that treatment. No other arrangement has been made for financial payments or other forms of compensation (such as lost wages, lost time or discomfort) with respect to such injuries. However, you do not waive any legal rights by signing this consent form.

During the study, if you experience any medical problems or illnesses, please contact Dr. _____ at ____ - ____ - ____.

What are your rights if you decide to participate in this study?

Your signature on this consent form means that you have received information about this study and that you agree to be a part of the study. If you decide to participate, you are free to discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. If you wish to stop your participation in this research study for any reason, you should contact Dr. _____ at ____ - ____ - _____. A decision to withdraw or to not take part in the study will not affect the quality of medical care that you receive. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled or affect your future medical care.

Your doctor or the sponsor, St Jude Medical, may decide to withdraw you from the study at any time without your consent. If certain circumstances arise and it is felt to be in your best interest, or if the study is discontinued, your doctor may withdraw you from this study. If you become ill during the research, you may have to be withdrawn from the study, even if you would like to continue. Your study doctor will make this decision.

If significant new findings are developed during the course of this study, your doctor will be notified immediately by St. Jude Medical and will advise you of such developments that may affect your willingness to continue your participation in this study.

You are making a decision as to whether or not to participate in the study. Your signature indicates that you have read the information provided above and have decided to participate in the study. You may withdraw at any time after signing this form should you no longer want to participate in this study.

Name of Patient (Please Print)

Signature of Patient **Date**

Signature of Person Obtaining Consent **Date**

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